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ORIGINAL ARTICLE **CME**

Using the Roach Formula to Stratify Patients with Localised Prostate Cancer Treated with Intensity-modulated Radiotherapy

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ABSTRACT

Objectives: *The Roach formula can be used to calculate the risk of pelvic lymph node involvement in patients with prostate cancer. This study aimed to use the Roach formula to further differentiate high-risk patients at risk of treatment failure after intensity-modulated radiotherapy (IMRT), and to identify factors associated with biochemical failure-free survival (bFFS).*

Methods: *Records of consecutive patients with biopsy-proven localised prostate cancer (T1-4 N0M0) who underwent prostate-only IMRT between February 2006 and August 2011 were retrospectively reviewed. Neoadjuvant and concomitant androgen deprivation therapy (ADT) was given to intermediate- and high-risk patients, whereas adjuvant ADT was given to high-risk patients for 2 to 3 years if they could afford this self-financed item. Patients were divided into three groups of lymph node involvement based on the Roach formula (≤15%, >15-35%, and >35% risk) and their bFFS were compared. Factors associated with bFFS were identified using univariate and multivariate analyses.*

Results: *The median follow-up duration of 144 patients was 55.8 months. According to the National Institute for Health and Care Excellence classification, 6%, 30%, and 64% of patients were stratified as low, intermediate, and high risk, respectively. According to the Roach formula, 35%, 28%, and 37% of patients were stratified as low, (≤15%), intermediate (>15-35%), and high (>35%) risk of lymph node involvement, respectively. Biochemical failure occurred in 23 patients. The median bFFS was 48.5 months. The 5-year bFFS in the three groups of ≤15%, >15-35%, and >35% risk of lymph node involvement based on the Roach formula were 100%, 87.7%, and 75.4%, respectively (p = 0.003). In multivariate analysis, significant factors associated with better bFFS were patient age of >75 years, pretreatment serum prostate-specific antigen (PSA) of ≤20 ng/ml, undetectable serum PSA after IMRT, and longer duration of adjuvant ADT.*

Conclusion: *The Roach formula can further differentiate patients at higher risk (>15-35% and >35%) of lymph node involvement to receive more intensified IMRT and closer monitoring to improve their bFFS.*

Key Words: *Neoplasm staging; Prostate neoplasms; Prostate-specific antigen; Radiotherapy, intensity-modulated*

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中文摘要

使用Roach公式區分接受調強放射治療的局部前列腺癌患者

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背景：Roach公式能計算前列腺癌患者的盆腔淋巴結受累風險。本文旨在利用Roach公式進一步區分接受調強放射治療（IMRT）後失敗的高風險患者，並確定與無生化失敗存活率（bFFS）的相關因素。

方法：回顧2006年2月至2011年8月所有接受前列腺IMRT的局部前列腺癌（T1-4 N0M0）患者。中高危患者被給予新輔助治療和抗雄激素治療（ADT），而高危患者（如能負擔）被給予2至3年輔助ADT。根據Roach公式，患者被分為三級淋巴結受累風險（≤15%、>15-35%、>35%），並比較其bFFS。與bFFS的相關因素用單變量和多變量分析來確定。

結果：共144例的中位隨診時間為55.8個月。根據NICE分類，6%、30%、64%的患者被分為低、中、高危。根據Roach公式，35%、28%、37%的患者被分為低（≤15%）、中（>15-35%）、高（>35%）淋巴結受累風險。23例患者生化失敗。bFFS中位數為48.5個月。基於Roach公式的≤15%、>15-35%、>35%的淋巴結受累風險，其bFFS分別為100%、87.7%、75.4%（p = 0.003）。在多變量分析中，與更佳bFFS的相關因素為患者年齡大於75歲、療前血清前列腺抗原（PSA）≤20 ng/ml、IMRT後血清PSA降低至檢測不到、及接受輔助ADT治療時間較長。

結論：Roach公式可進一步區分更高淋巴結受累風險（>15-35%和>35%）的患者以接受更強化的IMRT和更密切的監測來改善其bFFS。

INTRODUCTION

According to the Hong Kong Cancer Registry, prostate cancer is the third most common cancer in males, with 1631 new cases registered in 2012.[1] Its incidence among the age-group of 45 to 75 years is increasing.[1] Radiotherapy and surgery are standard treatments for early-stage localised prostate cancer. Intensity-modulated radiotherapy (IMRT) enables dose escalation and sparing of adjacent organs from unnecessary radiation, with improved efficacy and safety.[2] Nevertheless, it remains controversial about the role of whole-pelvic radiotherapy (WPRT) for high-risk prostate cancer owing to its treatment efficacy and toxicity profile.

The Roach formula (2/3 × prostate-specific antigen [PSA] + [Gleason score - 6] × 10) is used to predict the risk of pelvic lymph node involvement in prostate cancer patients.[3] A Roach score of <15% and ≥15% of lymph node involvement is considered low and high risk, respectively. WPRT is advocated for patients with high-risk pelvic lymph node involvement. Nonetheless, there is evidence that the Roach formula may overestimate the risk of nodal metastasis by 2.5 to 4.5 fold.[4-6] Some high-risk patients might be overtreated with WPRT. The treatment outcome in high-risk patients is diverse.[7,8] This study aimed to use the Roach formula to further differentiate high-risk patients at risk of treatment failure after IMRT, and to identify factors associated with biochemical failure-free survival (bFFS).

METHODS

The research protocol was conducted in compliance with Declaration of Helsinki. Records of consecutive patients with biopsy-proven localised prostate cancer (T1-4 N0M0) who underwent IMRT at our department between February 2006 and August 2011 were retrospectively reviewed.

Tumour staging was evaluated using digital rectal examination, transrectal ultrasonography, and contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Node and metastasis staging was evaluated using CT and MRI. Primary and secondary Gleason scores were assessed, as was serum PSA level. Patients with a PSA level of >20 ng/ml or clinical suspicion of metastasis were assessed using bone scan or positron emission tomography computed

tomography to rule out metastasis.

For target and organ-at-risk delineation in IMRT planning, patients were immobilised by a belly board in a prone position to minimise bowel toxicity and underwent CT with 3-mm slice thickness. If patients could not tolerate the prone position, they were immobilised in a supine position with Vac-Lok cushions. CT were co-registered with contrast-enhanced MRI for better delineation. The clinical and planning target volumes and organ-at-risk (the bladder, femoral necks, and rectum) were contoured, using the Eclipse Treatment Planning System version 8.9 (Varian Medical Systems, Palo Alto [CA], USA). According to the National Institute for Health and Care Excellence (NICE) classification, patients were stratified as low, intermediate, and high risk based on tumour staging, serum PSA level, and Gleason score.[9,10] The clinical target volume included the whole prostate gland for low-risk patients, and also the base of the bilateral seminal vesicles for intermediate-risk patients, and the whole seminal vesicles for high-risk patients. The planning target volume was expanded around 0.5 to 1 cm from all directions to accommodate body and organ motion and setup errors. Patients were treated with prostate-only IMRT without pelvic nodal irradiation. IMRT was optimised using an anisotropic analytical algorithm. A 7- to 8-field step-and-shoot IMRT plan was generated, and a total dose of 76 Gy in 38 daily fractions over 7.6 weeks for planning target volume was prescribed. Tumour position was verified with on-board imaging before IMRT and then before the first three fractions, and then weekly to track any displacement.

Neoadjuvant and concomitant androgen deprivation therapy (ADT) using a luteinising hormone-releasing hormone agonist was given to intermediate- and high-risk patients based on the NICE classification. ADT using flutamide 250 mg three times a day was administered 7 to 14 days and continued for 4 weeks to avoid testosterone flare-up. Adjuvant ADT (leuprorelin or triptorelin) was also given to high-risk patients every 3 months for 2 to 3 years if they could afford this self-financed item.

Table 1. Classification of patients to low, intermediate, and high risk based on the National Institute for Health and Care Excellence classification.

Risk group	Tumour staging	Prostate-specific antigen (ng/ml)	Gleason score
Low (n = 9)	cT1-2b	≤10	<7
Intermediate (n = 43)	cT2c	10-20	7
High (n = 92)	cT3-4	>20	>7

Patients were followed up weekly during IMRT to monitor for any side-effects, and 3 monthly thereafter with serum PSA monitoring. Biochemical failure was defined as a rise of serum PSA level by ≥2 ng/ml above the nadir.[11] bFFS was counted from the date of commencement of neoadjuvant ADT to the date of biochemical failure or death from any cause, whichever came earlier.

The bFFS was plotted using the Kaplan-Meier curve. The bFFS of three groups calculated as ≤15%, >15-35%, and >35% risk of lymph node involvement based on the Roach formula were compared using the log-rank test. These cut-offs could most differentiate patients into significantly different groups. Factors associated with better bFFS were identified using the univariate and multivariate (backward elimination) analyses. A p value of <0.05 (two-sided) was considered statistically significant. Patient stratification based on the NICE classification and the Roach formula were compared using the receiver operating characteristic (ROC) curve.

RESULTS

The median patient age was 74 (range, 50-84) years. One of the 144 patients with a missing Gleason score was excluded. Of the 143 patients, 90 were evaluated by MRI, 11 by CT, 7 by both MRI and CT, and 35 had no pretreatment imaging. All patients underwent transrectal ultrasonography and had 10 to 12 biopsies. The median follow-up duration was 55.8 (range, 9-92) months. According to the NICE classification, 6%, 30%, and 64% of patients were stratified as low, intermediate, and high risk, respectively (Table 1). According to the Roach formula, 35%, 28%, and 37% of patients were stratified as low, (≤15%), intermediate (>15-35%), and high (≤35%) risk of lymph node involvement, respectively (Table 2).

Biochemical failure occurred in 23 (16.0%) patients. The median bFFS was 48.5 months. The 5-year bFFSs in the three groups of ≤15%, >15-35%, and >35% risk of lymph node involvement based on the Roach formula were 100% (95% confidence interval [CI] = 100-100%), 87.7% (95% CI = 76.1-99.3%), and 75.4% (95% CI = 61.7-89.1%), respectively (p = 0.003, Figure 1). The overall 5-year bFFS was 86.8% (95% CI = 80.1-93.5%), whereas the 5-year cancer-specific survival and overall

Table 2. Comparison of patients with ≤15%, >15-35%, or >35% risk of lymph node involvement based on the Roach formula*.

Demographic / characteristic	Risk of lymph node involvement based on the Roach formula			
	≤15%	>15-35%	>35%	p Value
No. of patients	50 (35.0)	40 (28.0)	53 (37.0)	-
Age (years)	75.3	74.2	72.6	0.153
Follow-up (months)	52.1	60.5	57.4	0.015
Tumour staging				0.032
T1-T2b	33 (66.0)	16 (41.0)	19 (35.8)	
T2c	8 (16.0)	10 (25.6)	14 (26.4)	
T3-T4	9 (18.0)	13 (33.3)	20 (37.7)	
Gleason score				<0.001
2-6	45 (90.0)	8 (20.0)	7 (13.2)	
7	5 (10.0)	20 (50.0)	14 (26.4)	
8-10	0 (0)	12 (30.0)	32 (60.4)	
Pretreatment serum prostate-specific antigen (ng/ml)				<0.001
<10	25 (50.0)	6 (15.0)	1 (1.9)	
10-20	22 (44.0)	16 (40.0)	4 (7.5)	
>20	3 (6.0)	18 (45.0)	48 (69.6)	
Neoadjuvant and concomitant androgen deprivation therapy	27 (54.0)	36 (92.3)	52 (100)	<0.001
Duration (months)	5.4	6.0	6.3	
Adjuvant androgen deprivation therapy	6 (12.0)	16 (41.0)	38 (73.1)	<0.001
Duration (months)	0†	0†	30.3	
Undetectable serum prostate-specific antigen after intensity-modulated radiotherapy	27 (54.0)	31 (77.5)	41 (77.4)	0.015

* Data are presented as median or No. (%) of patients.
† No median value because % of patients is <50%.

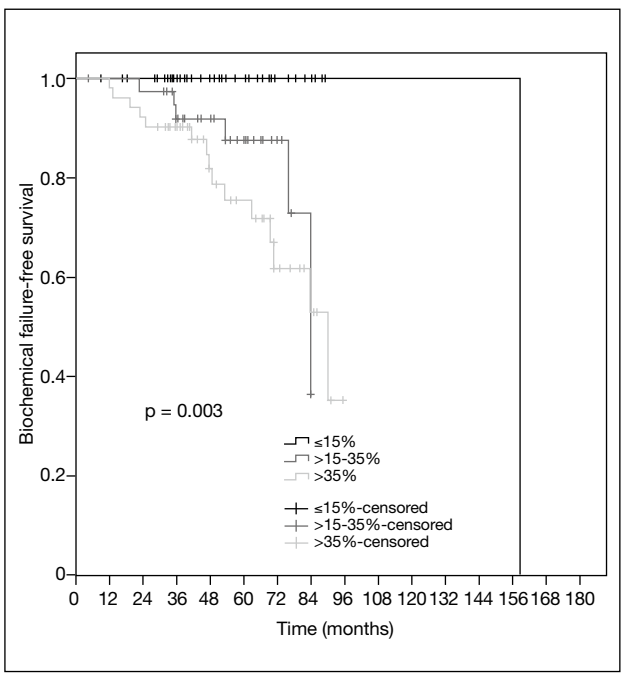

Figure 1. Kaplan-Meier curves for the biochemical failure-free survival in patients with ≤15%, >15-35%, and >35% risk of lymph node involvement based on the Roach formula.

survival were 98.3% and 92.1%, respectively (Figure 2).

In univariate analysis, significant factors associated with better bFFS were patient age >75 years, earlier tumour staging of T1-2b, Gleason score of ≤7, and pretreatment serum PSA of ≤20 ng/ml. In multivariate analysis, significant factors associated with better bFFS were patient age >75 years (hazard ratio [HR] = 0.071, p = 0.018), pretreatment serum PSA of ≤20 ng/ml (HR = 0.159, p = 0.017), undetectable serum PSA after IMRT (HR = 0.255, p = 0.016), and longer duration of adjuvant ADT (HR = 0.973, p = 0.043) [Table 3]. Of the 143 patients, 99 (69.2%) achieved a serum PSA of <0.1 ng/ml post-treatment.

The ROC curves for the risk groups based on the NICE classification and Roach formula were derived and found to be significantly different ($p < 0.01$). The concordance index for the Roach formula was higher than that for the NICE classification (0.724 vs. 0.715); higher concordance index indicated higher predictive power (Figure 3).

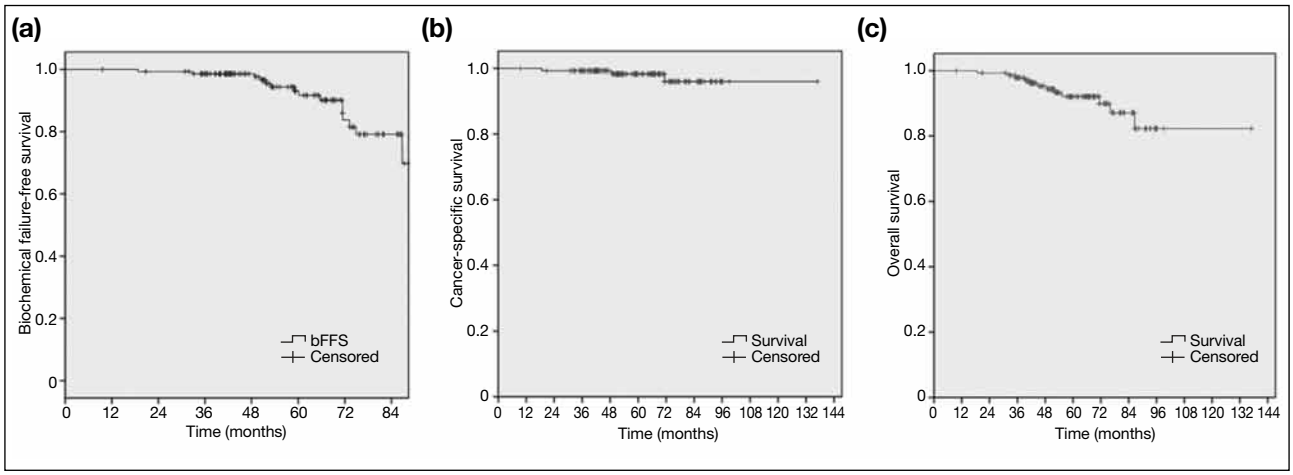

Figure 2. Kaplan-Meier curves for (a) overall biochemical failure-free survival, (b) cancer-specific survival, and (c) overall survival of the patients.

Table 3. Factors associated with better biochemical failure-free survival in multivariate analysis.

Factor	Hazard ratio (95% confidence interval)	p Value
Age >75 years	0.071 (0.008-0.632)	0.018
Presence of comorbidity	0.821 (0.286-2.357)	0.713
Tumour staging (T1-2b as reference)	2.584 (0.824-8.100)	0.103
Gleason score (≤7)	1.466 (0.511-4.204)	0.477
Pretreatment prostate-specific antigen (≤20 ng/ml)	0.159 (0.040-0.720)	0.017
Undetectable prostate-specific antigen after intensity-modulated radiotherapy (<0.1 ng/ml)	0.255 (0.084-0.771)	0.016
Achieving prostate-specific antigen nadir within 6 months after intensity-modulated radiotherapy	0.222 (0.022- 2.195)	0.198
Duration of neoadjuvant hormone therapy	0.999 (0.952-1.048)	0.970
Duration of adjuvant hormone therapy	0.973 (0.947-0.999)	0.043

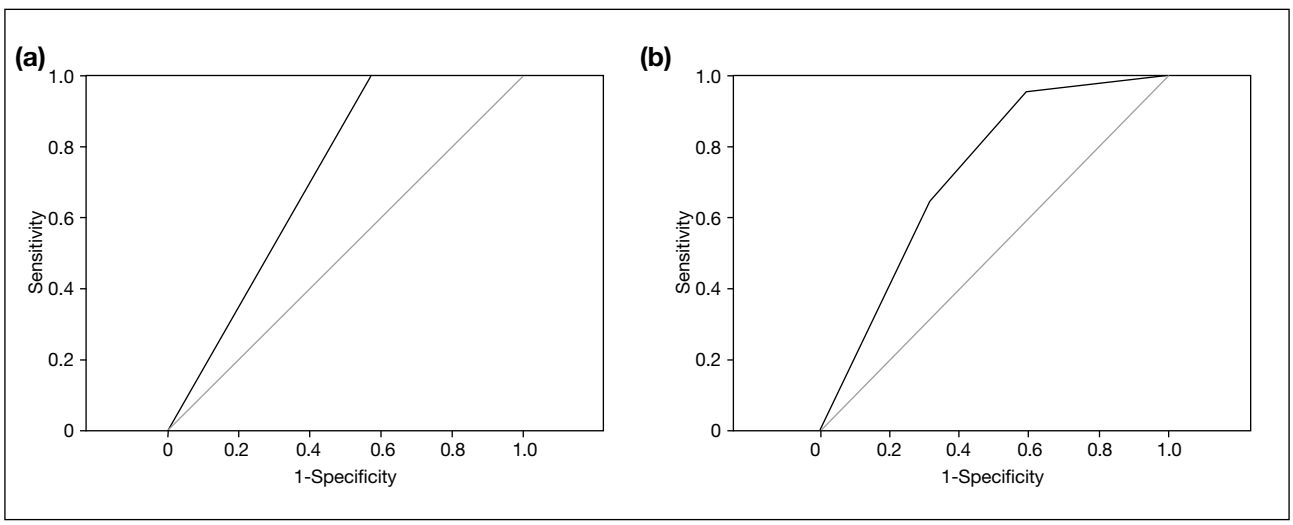

Figure 3. Receiver operating characteristic curves for the risk groups based on (a) the National Institute for Health and Care Excellence classification (concordance index = 0.715, p < 0.01), and (b) the Roach formula (concordance index = 0.724, p < 0.01). Higher concordance index indicates higher predictive power.

DISCUSSION

WPRT for prostate cancer aims to sterilise occult nodal metastasis and improve disease-free and overall survival of patients at high risk of nodal involvement.[12,13] Whether WPRT is indicated for high-risk patients is debatable as ADT can also tackle the same issue. According to the phase III trial of the Radiation Therapy Oncology Group 94-13, WPRT only showed a trend of improved progression-free survival or overall survival compared with prostate-only radiotherapy.[14,15] Of 1292 patients with >15% risk of lymph node involvement, 75% and 25% of patients were further stratified to have >15-35% and >35% risk of lymph node involvement, respectively.[14,15] However, there was no analysis of the difference in benefit of WPRT in these two groups. In 358 patients with a median follow-up of 52 months, WPRT with long-term ADT was recommended for patients with >30% risk of nodal involvement; nonetheless WPRT and prostate-only radiotherapy achieved comparable outcome in patients with lower nodal involvement.[7] In a study of 277 patients with >15% risk of lymph node involvement, WPRT and prostate-only radiotherapy achieved comparable bFFS ($p = 0.38$).[16] Some patients with high risk of lymph node involvement may benefit from prophylactic WPRT. Nonetheless, treatment outcome is diverse in studies of WPRT using lymph node involvement risk of >15% as a cut-off; further stratification to determine who may benefit most from WPRT is needed.[7,8,15,16] In our study, patients with >15% risk of lymph node involvement were sub-classified into those with >15-35% and those with >35% risk of lymph node involvement. The bFFS was significantly higher in patients with >15-35% than >35% risk of lymph node involvement (87.7% vs. 75.4%). Patients with metastasis to the lymph node were excluded.

Patients with undetectable serum PSA after radiotherapy is associated with better prognosis, biochemical recurrence-free survival (in patients after prostatectomy), and biochemical relapse-free survival (in patients after prostatectomy and salvage radiotherapy).[17,18] In our study, patient age >75 years was associated with better prognosis. This is contrary to other studies reporting advanced age as a poor prognostic factor in most types of cancer.[19-21] One postulation was that prostate cancer in younger patients might harbour a more aggressive clinical behaviour. Another postulation was that more PSA screening in older patients may result in earlier detection and stage migration. In addition, longer duration of adjuvant ADT was also associated with better prognosis, consistent with other studies.[22,23] We recommended 2 to 3 years of adjuvant ADT for high-risk patients. However, only 73% of our patients with >35% risk of lymph node involvement underwent adjuvant ADT (a self-financed item) for a median duration of 30 months.

The main limitations of our study were its retrospective nature and small sample size in a single institution. Nevertheless, the median follow-up duration was relatively long (about 5 years) and the radiotherapy technique and dose were standardised. Further studies on benefits of WPRT or more intensified IMRT for patients at higher risk (>15-35% and >35%) of lymph node involvement based on the Roach formula are warranted.

CONCLUSIONS

The Roach formula can further differentiate patients at higher risk (>15-35% and >35%) of lymph node involvement to receive more intensified IMRT and closer monitoring to improve their bFFS.

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